REMARKS

The pending claims are claims 1, 3-8, 13, 15 and 18-21. Claims 18-21 are new compound claims that depend directly from claim 1, which was previously elected for examination. As such, claims 18-21 should be examined with claims 1, 3-8, 13, and 15.

Support for new claims 18-21 can be found in claim 6 as filed, specifically substituent Nos. 5, 6, 7 and 10.

No new matter has been added herein.

Restriction/Election

Applicants respectfully request rejoinder of method claims 16 and 17 upon allowance of the product claims 1, 3-8, 13, 15 and 18-21.[1]

Rejection of Claims and Transversal Thereof

In the September 1, 2009 Office Action:

claims 1-12 and 18-29 were rejected under 35 U.S.C. §112, second paragraph;

claims 1, 3, ,4, 8 and 13 were rejected under 35 U.S.C. §102(b) as being anticipated by Bailey (U.S. Patent No. 4,206,215);

claims 1-4 and 8 were rejected under 35 U.S.C. §102(b) as being anticipated by Campos et al. (*Il Farmaco*, 58, 221-229 (2003));

claims 1-4, 8 and 13 were rejected under 35 U.S.C. §102(b) as being anticipated by Conejo-García et al. (*Eur. J. Med. Chem.*, 38, 109-116 (2003));

claims 1-4, 8 and 13 were rejected under 35 U.S.C. §102(b) as being anticipated by Campos et al. (*Bioinorg. Med. Chem.*, 10, 2215-2231 (2002)); and

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[1] Rejoinder was previously requested in the response to the May 6, 2009 Office Action, filed June 8, 2009.

claims 1-4, 8 and 13 were rejected under 35 U.S.C. §102(b) as being anticipated by Galanakis et al. (*J. Med. Chem.*, 38, 3536-3546 (1995)).

These rejections are respectfully traversed. The patentable distinctions of the pending claims over the cited references are set out in the ensuing discussion.

Rejections under 35 U.S.C. §112

In the September 1, 2009 Office Action, claims 1-12 and 18-29 were rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as his invention. Applicants traverse such rejection.

Specifically, the Examiner objected to the following issues:

1. The Examiner suggested that claims 1 and 13 should be amended to excise the term "general." Claims 1 and 13 have been amended accordingly.

2. The Examiner suggested that claims 2-7 and 13 should be amended to replace the phrase "characterized in that" with "wherein." Claims 2-7 and 13 have been amended accordingly.

3. With regards to claim 8, the Examiner questioned if a pharmaceutical composition was intended. Applicants have amended claim 8 to recite "pharmaceutical composition" instead of "pharmaceutical formulation."

4. With regards to claim 13, the Examiner indicated that the term "derivative" is indefinite. Applicants have excised said term, thereby obviating this rejection.

5. The Examiner suggested that claim 15 should be amended to replace the term "compounds" with "the compound." Claim 15 has been amended accordingly.

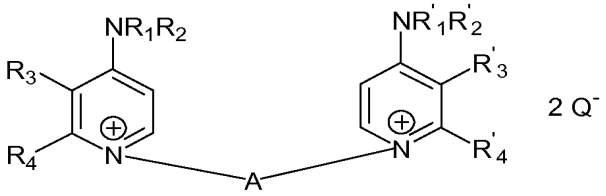
Withdrawal of the rejections under 35 U.S.C. §112, second paragraph, is respectfully requested.

Rejections under 35 U.S.C. §102

1. In the September 1, 2009 Office Action, claims 1, 3, 4, 8 and 13 were rejected under 35 U.S.C. §102(b) as being anticipated by Bailey (U.S. Patent No. 4,206,215). Applicants traverse such rejection.

Claim 1 has been amended to recite, *inter alia*:

1. A compound having formula I:

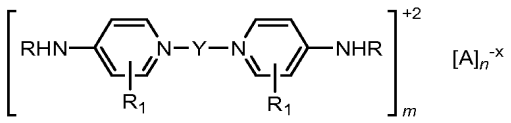


I

where

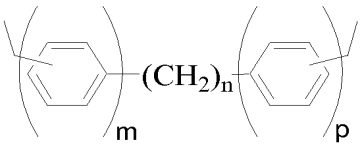
Q^-	**represents the conjugate base of a pharmaceutically suitable organic or inorganic acid;**
R_1 and R'_1	**represent, independently of each other, a radical selected from the group formed by H and C_{1-6} alkyl optionally substituted by trifluoromethyl, hydroxyl or alkoxyl;**
R_2 and R'_2	**represent, independently of each other, an aryl radical substituted by halogen, trifluoromethyl, hydroxyl, C_{1-6} alkyl, amino or alkoxyl** . . . . (emphasis added)

Bailey relates to antibacterial and antimicrobial compounds of the following formula:



wherein the spacer group, radical Y, is defined as "an alkylene group containing form 4 to 18 carbon atoms…" (see, Bailey, col. 2, lines 59-61). In column 6, lines 10-36, it is further detailed that "[i]n the formulas herein the alkylene group Y is a bivalent saturated aliphatic hydrocarbon radical containing from 4 to 18, preferably from 8 to 12, carbon atoms arranged in a straight or in a branched chain and separating the two 4-(R-NH)-1-pyridinyl groups by from 4 to 18, preferably from 8 to 12, carbon atoms, for example: …", followed by a list of several saturated aliphatic hydrocarbon radical examples.

In contrast, the spacer group in the compounds of the present invention, radical A, is defined as a compound of formula II:

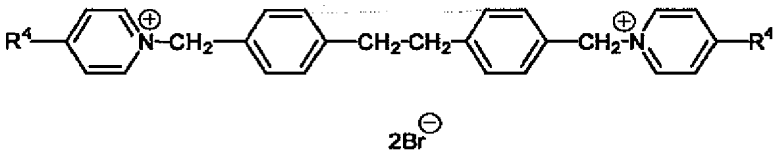


wherein m, n and p represent integers which can have the following values: m = 1; n =0, 1-10; p = 0, 1. In other words, the spacer group in the compounds of claim 1 ("Y") contains at least one phenyl ring, i.e., an aromatic (unsaturated) hydrocarbon radical, while the Bailey spacer ("A") is a saturated aliphatic hydrocarbon structure. Clearly, the Bailey saturated aliphatic hydrocarbon spacer does not anticipate applicants' claimed aromatic hydrocarbon radical spacer. Accordingly, none of the compounds disclosed in Bailey anticipate instant claim 1, or the claims depending therefrom.

Withdrawal of the novelty rejection in view of Bailey is respectfully requested.

2. In the September 1, 2009 Office Action, claims 1-4 and 8 were rejected under 35 U.S.C. §102(b) as being anticipated by Campos et al. (*Il Farmaco*, 58, 221-229 (2003)) (hereinafter Campos I). Applicants traverse such rejection.

Campos I describes bisquaternary heterocyclic compounds with Choline Kinase inhibitory activity, with example 3k as the closest structure to the claimed compounds of the invention. For ease of reference, example 3k corresponds to the following formula wherein R^4 is NMePh.

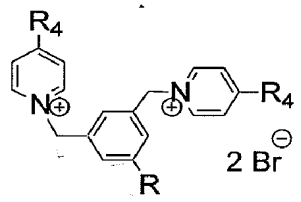


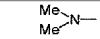
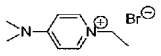
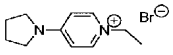
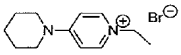
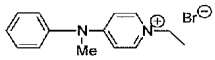
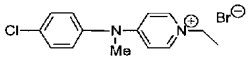
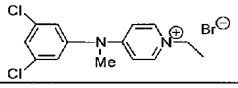
None of the compounds in Campos I have an "aryl radical substituted by halogen, trifluoromethyl, hydroxyl, C_{1-6} alkyl, amino or alkoxyl" in the position corresponding to radicals R_2 and R_2' in the claimed compounds of the invention. As a consequence, the examples described in Campos I do not anticipate presently claimed formula I.

Withdrawal of the novelty rejection in view of Campos I is respectfully requested.

3. In the September 1, 2009 Office Action, claims 1-4, 8 and 13 were rejected under 35 U.S.C. §102(b) as being anticipated by Conejo-García et al. (*Eur. J. Med. Chem.*, 38, 109-116 (2003)) (hereinafter Conejo-García). Applicants traverse such rejection.

Conejo-García relates to ChoK inhibitors, wherein compounds 5 and 9-11 are structurally related to the compound of applicants' claim 1.



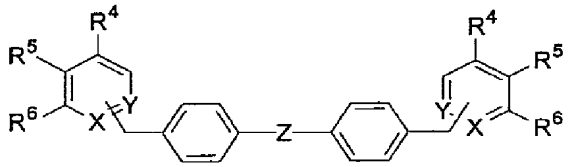
Compound	R_4	R
2		H
3		H
4		H
5		H
6		
7		
8		
9		
10		
11		

In can be seen that compounds 5 and 9 in Conejo-García do not anticipate the compounds of applicants' claim 1 because they do not contain a substituted aryl group in the position corresponding to radicals R_2 and R_2'. Further, none of examples 5 and 9-11 teach applicants' spacer group "A." As a consequence, the examples described in Conejo-García do not anticipate presently claimed formula I.

Withdrawal of the novelty rejection in view of Conejo-García is respectfully requested.

4. In the September 1, 2009 Office Action, claims 1-4, 8 and 13 were rejected under 35 U.S.C. §102(b) as being anticipated by Campos et al. (*Bioinorg. Med. Chem.*, 10, 2215-2231 (2002)) (hereinafter Campos II). Applicants traverse such rejection.

Campos II discloses compounds 57-59 as Choline Kinase inhibitors.



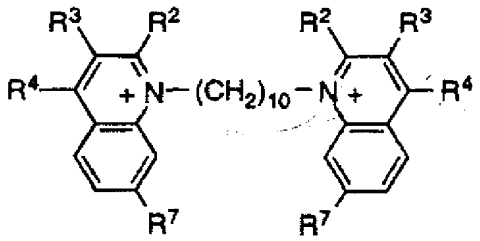
Compd.	X	Y	R^4	R^5+R^6	Z
60	N^+	CH	$-NC_6H_{12}$[e]	2H	$(CH_2)_3$
61	N^+	CH	$-N(Allyl)_2$	2H	$(CH_2)_3$
62	N^+	CH	$-NC_6H_{12}$[e]	2H	CH_2
57	N^+	CH	–N(Me)Ph	2H	CH_2
58	N^+	CH	–N(Me)Ph	2H	$(CH_2)_2$
40	CH	N^+	–H	$(CH=CH)_2$	$(CH_2)_3$
59	N^+	CH	–N(Me)Ph	2H	$(CH_2)_3$

It can be seen that the Campos II compounds have an unsusbtituted aryl group, instead of an "aryl radical substituted by halogen, trifluoromethyl, hydroxyl, C_{1-6} alkyl, amino or alkoxyl" in the position corresponding to radicals R_2 and R_2', as claimed by applicants herein. As a consequence, the examples described in Campos II do not anticipate presently claimed formula I.

Withdrawal of the novelty rejection in view of Campos II is respectfully requested.

5. In the September 1, 2009 Office Action, claims 1-4, 8 and 13 were rejected under 35 U.S.C. §102(b) as being anticipated by Galanakis et al. (*J. Med. Chem.*, 38, 3536-3546 (1995)) (hereinafter Galanakis). Applicants traverse such rejection.

Galanakis describes bis-quinolinium derivatives as potassium channel blockers, specifically compounds 8 and 9.



compd	R^2	R^3	R^4	R^7
1	H	H	$NHCH_2Ph$	H
2	H	H	$NHCH_2Ph$	NH_2
3	$CH_2CH_2-CH_2CH_2$		NH_2	H
dequalinium (**4**)	CH_3	H	NH_2	H
5	H	H	Y[d]	H
6	H	H	NH_2	H
7	H	H	$N(CH_3)_2$	H
8	H	H	$N(CH_3)Ph$	H
9	H	H	NHPh	H

Galanakis does not teach any compound wherein the aryl group in the position corresponding to radicals R_2 and R_2' is substituted. Further, none of compounds 8 or 9 teach applicants' spacer group "A." As a consequence, the examples described in Galanakis do not anticipate presently claimed formula I.

Withdrawal of the novelty rejection in view of Galanakis is respectfully requested.

It is noted that none of the references cited by the Examiner make obvious applicants' claimed invention. Campos I (compound 3k), Conejo-García (compounds 5 and 9) and Campos II (compounds 57-59) can be considered as the closest prior art documents. Each disclose at least one compound having a similar core structure as the claimed compounds of the invention, except for the radical at position R_2 and R_2' (and in some cases the spacer group). As discussed hereinabove, R_2 and R_2' in the compounds in Campos I, Conejo-García and Campos II are unsubstituted aryl radicals, whereas in applicants' claim 1, R_2 and R_2' are substituted aryl groups.

Firstly, none of the cited documents motivates, teaches or suggests substituting at position R_2 and R_2' of the claimed compound. In fact, the skilled person would not have found any guidance in the teaching of the prior art documents, considered alone or in combination, to arrive at the presently claimed invention.

In addition, the substitution at position R_2 and R_2' of the claimed compound, unexpectedly resulted in a dramatic improvement in *in vivo* activity and toxicity, compared to the corresponding derivatives wherein the radical at R_2 and R_2' is non-substituted (i.e., the compounds of the prior art). Applicants have included herewith an affidavit under 37 CFR 1.132 including the results of comparative experiments (**Appendix A**). Specifically, it can be clearly seen that non-substituted compound **2** shows a remarkably higher toxicity (lower Lethal Dose value) than the substituted compounds of the presently claimed invention (compounds **1**, **3-10**). In addition, non-substituted compound **2** presents very low (5D schedule) or no (1D schedule) *in vivo* antitumoral activity, while the presently claimed

compounds (compounds **1**, **3-10**) show notably high *in vivo* antitumoral activity according to both 5D and 1D schedule.

Accordingly, the applicants' claims are non-obvious in view of the cited prior art.

Petition for Extension of Time/Fees Payable

Applicants hereby petition for a one (1) month extension of time, extending the deadline for responding to the September 1, 2009 Office Action from December 1, 2009 to January 4, 2009.

Four (4) dependent claims have been added herein, bringing the total number of claims to fifteen (15), one (1) of which is independent. As such, no added claims fee is due at this time.

The total fee of $65.00 specified in 37 C.F.R. §1.17(a)(1) for said one (1) month extension is being paid by Electronic Funds Transfer. Authorization is hereby given to charge any deficiency in applicable fees for this response, or credit any overcharge, to Deposit Account No. 13-4365 in the name of Moore & Van Allen, PLLC.

Conclusion

The claims are in form and condition for allowance. If any additional issues remain, the Examiner is requested to contact the undersigned attorney at (919) 286-8000 to discuss same.

Respectfully submitted,

MOORE & VAN ALLEN PLLC

Date: December 24, 2009

By: _____

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